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Amylin Signaling in Diabetes and Alzheimer's Disease: Therapy or Pathology?

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Abstract

Growing evidence highlights the intimate relationship between type II diabetes (T2D) and Alzheimer's disease (AD). Importantly, these two diseases share a number of pathological similarities, including amyloid accumulation, oxidative stress, inflammation, and cell death. To date, drug therapies for AD and T2D are lacking and there is a crucial need for the discovery and development of novel therapeutics for these diseases. A number of human and rodent studies have given evidence that metabolic hormone supplementation is highly valuable for improving cognitive function and overall metabolic health in both T2D and AD. The pancreatic hormone amylin has arisen as a crucial component of the disease etiology of both T2D and AD, though the exact role that amylin plays in these diseases is not yet well understood. Here, we critically review the current literature that utilizes human amylin or its synthetic analogue, pramlintide, as well as amylin receptor antagonists for the treatment of AD.

Introduction

Alzheimer's disease (AD) is a progressive, debilitating neurodegenerative disease characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau[1]. The accumulation of these pathological peptides contributes to deficits in executive functions such as learning and memory, mood, affect, etc. and presents a substantial burden to the patient and caregivers. The incidence of AD is increasing at an alarming rate in the U.S., with an estimated 5.5 million Americans living with AD as of 2017 and this number is expected to triple by 2050[2]. Furthermore, the cost of caring for and treating AD patients currently exceeds $200 billion annually and is only expected to increase[3]. While AD is clearly a monumental problem within the U.S. and beyond, treatment options remain very limited[4]. Many drug trials have been conducted with a wide array of targeted approaches, yet there are currently only six drugs approved by the FDA for AD and are only symptomatic treatments[5,6]. To date, the majority of pharmacological agents developed have specifically targeted the hallmark Aβ or tau pathology, yet none have been successful in clearing or preventing pathology[4]. As such, there is a fundamental need to develop viable therapeutics and preventative treatments for AD.

Age-related (sporadic) AD is a complicated multifactoral disease, having numerous genetic and environmental influences. Environment and lifestyle are heavily implicated in the development of sporadic AD; factors such as diet[7-9], obesity[8-10], metabolic syndrome[7], type II diabetes (T2D)[9,11], and cardiovascular disease[12] have all been implicated in the causation of AD. Of critical importance, rates of obesity and diabetes are rapidly rising in parallel with AD[12,13]. Though the relationship between obesity and AD is

somewhat unclear, there is evidence that mid-life obesity plays a role in the development of AD[10]. More importantly, obesity is commonly accompanied by a number of other diseases, including cardiovascular disease, hypertension, dyslipidemia, T2D, stroke, etc.[14]. The incidence of T2D is quickly rising, with the CDC estimating that approximately 30.3 million people (1 in 10 adults) in the U.S. have diabetes and a staggering 84.1 million (1 in 3 adults) have prediabetes, most of whom are unaware of their condition. Furthermore, due to a large-scale decrease in physical activity that is accompanied by a simultaneous increase in food intake and poor diet, rates of obesity, T2D, metabolic syndrome, and cardiovascular disease are only proposed to increase to an estimated 600 million T2D cases worldwide by 2035[15].

The body of evidence implicating metabolic function and disease in the process of cognitive decline and aging is substantial[16, 17]. For example, approximately 70% of people diagnosed with T2D report cognitive impairment and a substantial number of T2D patients later develop dementia[16, 18-21]. Individuals diagnosed with T2D for at least five years have a significantly increased risk of developing AD compared to those whom have suffered from T2D for less than five years[17]. Together these data suggest that the increasing prevalence of T2D in the population may be contributing to the rising rates of AD.

T2D is initially characterized by high blood glucose and insulin, which leads to hyperinsulinemia; importantly, amylin, a small metabolic hormone produced by β-islet cells of the pancreas, is co-packaged and co-secreted with insulin and is thus overproduced in T2D.[22]. Importantly, there are a number of pathological features that are present in both T2D and AD: 1) decreased brain metabolism and metabolic hormone resistance 2) amyloid pathology 3) oxidative stress (OS) and inflammation. Chronic, hyperinsulinemia and hyperamylinemia leads to a number of physiological issues: chronic hyperinsulinemia leads to system insulin resistance[22], impaired insulin transport across the blood-brain barrier (BBB)[23, 24], and thus decreased insulin signaling within the brain[25]. Loss of insulin signaling in the brain is associated with a number of AD-related pathological features, including increased Aβ production, tau phosphorylation, and neuroinflammation.

Furthermore, amylin shares similar pathological features with Aβ at high concentrations[26] and may be a common pathway between the two diseases. For example, amylin fibrils have been found in the pancreas of 95% of T2D patients[27-29] and cause a number of physiological disruptions including aberrant Ca^{2+} influx, increased secretion of pro-inflammatory cytokines[30,31], and ultimately β-islet cell loss[32]. Furthermore, amylin readily crosses the BBB and forms amylin fibrils as well as mixed plaques with Aβ within the brain and may be responsible for AD-like pathology and Aβ seeding in T2D[33-35]. Amylin is known to affect long-term potentiation (LTP) in the hippocampus and may have an innate influence on cognitive function within the brain[36-39]. However, whether amylin is a toxic insult in these diseases or whether its functional loss through aggregation or late stage β-cell loss in T2D contributes to the development of an AD remains unclear.

The Amylin Signaling Dichotomy

There is still much debate about the involvement of the amylin receptor (AMY_R) and amylin signaling in the disease progression and etiology of T2D and AD. The body of research aimed at discerning this relationship is quickly expanding. All relevant research has consistently demonstrated that modulation of amylin signaling affects AD-related pathology. The nature of this relationship, however, has yet to be concretely elucidated. Several groups have produced compelling data suggesting that amylin signaling is beneficial in preventing AD-related pathology and cognitive deficits both *in vivo* and *in vitro*[40-44]. Importantly, pramlintide, a recombinant non-aggregating form of amylin, used in conjunction with insulin therapies to treat diabetes and improves glycemic control, reduces body weight, and reduces serum markers of OS[45-47] also shows promise as an AD therapeutic. To date, however, there have been no clinical trials that have aimed to utilize amylin or pramlintide as a therapeutic agent in treating dementia. Clear evidence from rodent studies suggests that chronic treatment with either human amylin or pramlintide poses strong therapeutic benefit in reducing AD-related pathology; amylin/pramlintide supplementation reduces soluble Aβ levels, plaque burden, tau phosphorylation, neuroinflammation, and OS while also improving cognition[40-42,44]. The above data suggest that a loss of innate amylin signaling in the CNS due to aggregation gives rise to an increased risk for the development of AD and is covered in more detail in Grizzanti et al. 2018[48].

In contrast, studies also show that human amylin and Aβ have similar toxic effects and that these toxic effects can be alleviated using AMY_R antagonist[36-39,49]. For example, data show that *in vivo* treatment with AMY_R antagonists yields very similar physiological benefits to amylin or pramlintide treatment. Treatment of TgCRND8 AD mice with AC253, an AMY_R antagonist, or its cyclic counterpart cAC253 reduces neuroinflammation, soluble Aβ levels, and plaque burden while also improving cognition[50]. Similarly, *in vitro/ex-vivo* studies show that low dose human amylin or Aβ causes disruptions in LTP and that these deficits are blocked by AC253 or pramlintide[38,39], and higher doses of human amylin/amylin oligomers are associated with uncontrolled Ca^{2+} influx, which is strongly linked to cell death[26,32]. Together, these data support a toxic function of amylin oligomers and thus a potential therapeutic mechanism for AMY_R blockade. In contrast, others have shown that the beneficial effects of amylin can be blocked using AC253[41]. Thus, the therapeutic

potential of amylin treatment or inhibition remains unclear and highlights the complex and dichotomous nature of amyloids in the brain and periphery.

Piecing Together the Puzzle

There are a number of holes in the current literature that need filling to give a more complete picture of the amylin story: 1) the nature of the innate amylin system and amylin signaling within the brain 2) Aβ and pramlintide signaling capabilities through the three main AMY_R and related receptors 3) the therapeutic mechanisms by which amylin/pramlintide or AMY_R inhibition are mediated. First, interesting novel data demonstrate that the AMY_R is not only involved in signaling, but also in ligand transport across the BBB. The AMY_R is a heterodimeric receptor that is composed of a calcitonin receptor and a receptor activity modifying protein (1-3)[51]. To this end, a 50% global knockdown of the calcitonin receptor (a key component of the AMY_R) significantly reduced the amount of AC253 found in the brain[50], indicating that AMY_R located in the BBB are involved in transporting these ligands into the brain and may also be involved in shuttling amylin and pramlintide into/out of the brain. The existence of these BBB transport mechanisms suggests that amylin likely has innate physiological function in the brain, as its transport into the brain is tightly controlled. However, how amylin signaling or lack thereof leads to the pathological features of AD and whether the AMY_R is the vehicle through which Aβ mediates its toxic effects still remains unclear.

Next, conflicting evidence exists with regard to the relationship between Aβ and the AMY_R. Though several studies clearly demonstrate that human amylin and Aβ have similar effects on LTP in the CNS and use of AMY_R inhibitors ameliorates these deleterious effects[36-39], other evidence suggests that Aβ (1-42) is incapable of signaling through the any of the AMY_R to evoke any sort of cAMP response at a wide variety of concentrations[52]. It is possible that Aβ activates different signaling cascades through interaction with the AMY_R or simply acts as an inert competitive inhibitor, but this has yet to be demonstrated.

Furthermore, a separate study demonstrated that oligomeric amylin mediates its toxic effects directly through the AMY_R and indirectly through TRPV4, a nonselective cation channel[26]. Low concentrations to of human amylin evoke a Ca^{2+} response that is mediated through its native receptor. However, at higher concentrations, human amylin forms oligomers and actives aberrant signaling that results in the activation of TRVP4 channels and allows for uncontrolled cation influx, particularly Ca^{2+}. Pharmacological blockade of the AMY_R and TRPV4 demonstrates that both receptors are necessary for oligomeric human amylin to induce its toxic Ca^{2+} effects[26]. As such, it is likely that Aβ mediates its toxic effects on the AMY_R in a similar fashion, though these data do not yet exist. Uncontrolled Ca^{2+} influx is linked to a number of pathological phenomena, including uncontrolled vesicular release, OS and mitochondrial dysfunction, apoptosis, etc. To this end, it is likely that cellular dysfunction and the development of additional AD-like pathology that arises from toxic amyloid signaling is mediated through both the AMY_R and TRPV4. As such, it is necessary to discern the signaling cascades that modulate the relationship between the AMY_R and TRVP4. Furthermore, pharmacological experiments are warranted that utilize Aβ and pramlintide over a wide array of doses to determine Aβ and pramlintide's effects on Ca^{2+} currents, LTP, cAMP production, and other signaling cascades to determine their signaling capabilities. These experiments will help to fill some of the voids in the current literature with regard to the AMY_R and its involvement in disease states (Figure 1).

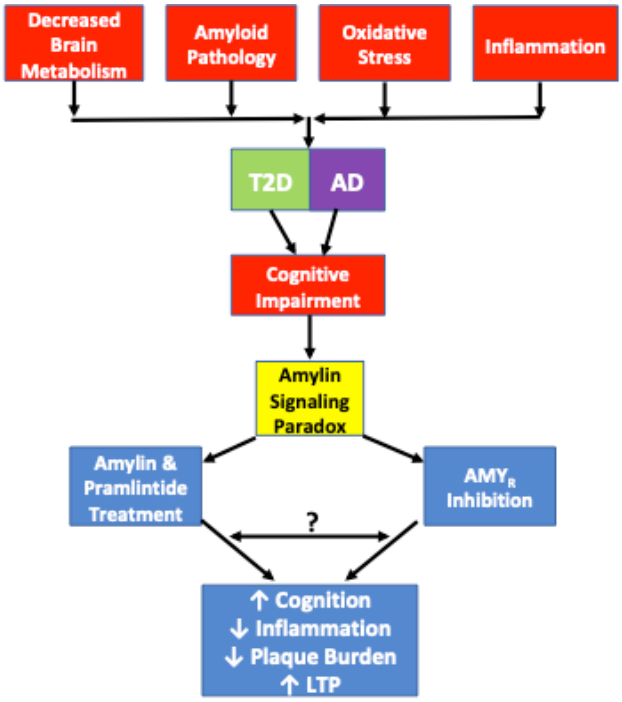

Figure 1 depicts the amylin signaling paradox and pathological similarities observed in T2D and AD. Decreased brain metabolism, amyloid pathology, oxidative stress and inflammation are all common pathological features observed in both diseases. While not every case of T2D or AD includes each of these pathological features, every case exhibits cognitive impairment. The amylin signaling paradox comes in to play as studies have shown that both AMY_R inhibition and AMY_R agonism via amylin and pramlintide treatment results in improved cognition, decreased inflammation, decreased plaque burden and increased LTP. The signaling mechanisms governed by AMY_R agonism and AMY_R antagonism have yet to be fully elucidated. While amylin signaling is traditionally associated with cAMP and PKA signaling, it is unclear if other cascades are also activated by amylin/pramlintide. Furthermore, it is unclear if AMY_R antagonists, amylin oligomers, or Aβ signal through the AMY_R or whether there are any similarities or crosstalk between all of these AMY_R ligands. As such, a number of experiments proposed in this review will help to further elucidate the true nature of the AMY_R.

Conclusions

The current disparity with regard to the role of amylin signaling in the brain demonstrates an essential need for further elucidation of amylin's involvement in both AD and T2D. In T2D, it is likely that in the early stages of the disease, amylin floods the brain, forms oligomers, induces aberrant signaling through its native receptor, and recruits TRPV4 to induce pathological Ca^{2+} influx that results in widespread neuronal dysfunction that manifests as OS, uncontrolled vesicular release and interneuronal dysfunction, inflammation, and resulting cell death. This mechanism may be responsible for the initial transition from the healthy brain to brain aging in metabolic disease. As such, AMY_R or TRVP4 inhibition at certain time points in metabolic disease and in the early stages of diabetes may be warranted to block the toxic effects of oligomeric amylin or Aβ. However, strong evidence also suggests that amylin replacement with either human amylin or pramlintide reduces most of the major AD related pathology while also improving cognition in rodent models of AD. As such, amylin signaling replacement with amylin or pramlintide in the mid to late stages of diabetes when amylin signaling is lost due to aggregation, oligomerization, or β-cell loss may be warranted. To this end, there is also a need to discern the temporal presentation of pathological events in metabolically linked brain aging and therapeutic options for early, intermediate, and late stage disease. Critical analysis and testing of the direct nature and signaling capabilities of these amyloids as well as the therapeutic nature of specific temporal treatments may help to bridge the gap between AMY_R inhibition therapies and amylin replacement therapies.

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